Diagnostic Snapshot

Knowing Your Target: Altered Mental Status From an Unsuspected Source

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Abstract

Daratumumab is a human monoclonal antibody targeting CD38 that is used in the treatment of multiple myeloma. In addition to being a target for cancer-related treatment, CD38 also plays a significant role in the immune response to infection. CD38 deficiency can increase susceptibility to several bacterial infections. This article discusses the case of a 52-year-old female with a history of IgG multiple myeloma status post autologous stem cell transplant with relapse who was receiving therapy with daratumumab, lenalidomide, and dexamethasone. She presented to the emergency department with a history of 3 to 4 days of generalized weakness, poor appetite, nausea, vomiting, watery stools, and fevers. Her symptoms did not improve with initial fluid resuscitation and broad-spectrum antimicrobials; instead, she experienced progressive neurological decline. This case illustrates how utilizing targets for cancer-directed treatments can also affect immune function, which may leave patients susceptible to unique infections that may not otherwise be commonly encountered. Therefore, advanced practitioners must understand the functional role of these targets and the sequelae that could occur when expression is altered by pharmacological therapies to allow for expeditious recognition and management.

HISTORY AND CHIEF COMPLAINT

KS is a 52-year-old female with a history of chronic kidney disease, hypertension, and relapsed IgG kappa multiple myeloma who is postautologous stem cell transplant and receiving therapy with daratumumab (Darzalex), lenalidomide, dexamethasone, and denosumab. KS presented to the emergency department with symptoms that included 3 to 4 days of generalized weakness, poor appetite, nausea, vomiting, and watery, nonbloody stools. She denied fevers or chills at home but was noted to be febrile at 38.8°C in triage. The remainder of the review of systems was negative. At the time of presentation, she was taking acyclovir as prescribed by her oncologist for prophylaxis.

PHYSICAL EXAM AND DIAGNOSTIC WORKUP

On initial exam, KS was alert and oriented × 4. She endorsed generalized weakness, but her neurological exam was otherwise intact without focal findings. She was noted to be slightly tachycardic, which improved following fluid resuscitation. Her breath sounds were clear to auscultation bilaterally and her abdomen was soft and nontender. She had no lower extremity edema, and her skin was warm and dry without any rashes.

The urinalysis was not suggestive of infection, and stool studies were ordered but were not collected, as her loose stools had stopped upon admission (Tables 1 to 3). The blood cultures were

collected on arrival and prior to starting antibiotics. A chest x-ray on admission was unremarkable.

Table 1. Initial Complete Blood Count

Lab	Reference range	Value
WBC	4.5–11.0 K/µL	**1.8 K/µL**
RBC	3.9–5.10 M/µL	**3.47 M/µL**
Hemoglobin	11.9–15.7 g/dL	**11.5 g/dL**
Hematocrit	35%–45%	**33.2%**
Platelets	153–367 K/µL	**100 K/µL**
Neutrophils	33%–75%	65%
Lymphocytes	15%–60%	20%
Monocytes	0%–9%	7%
Abs neutrophil	1.7–7.3 K/µL	**1.31 K/µL**
Bands	0%–5%	**8%**

Note. Bolded values indicate values outside of the defined reference range. WBC = white blood cell; RBC = red blood cell; Abs neutrophil = absolute neutrophil.

Table 2. Initial Chemistry Panel

Lab	Reference range	Value
Sodium	135–145 mmol/L	**130 mmol/L**
Potassium	3.5–5.1 mmol/L	**3.4 mmol/L**
Chloride	98–107 mmol/L	**93 mmol/L**
CO_2 total	21–30 mmol/L	**18 mmol/L**
Anion gap	4–16	19
BUN	7–17 mg/dL	**48 mg/dL**
Creatinine	0.70–1.50 mg/dL	**3.13 mg/dL** (baseline 1.2)
Glucose	74–106 mg/dL	87 mg/dL
Calcium	8.4–10.2 mg/dL	**7.2 mg/dL**
Phosphorus	2.5–4.5 mg/dL	2.8 mg/dL
Total protein	6.3–8.2 mg/dL	7.4 mg/dL
Albumin	3.5–5.0 mg/dL	3.7 mg/dL
Ionized calcium	1.15–1.29 mmol/L	**0.92 mmol/L**
Lactate	0.5–2.2 mmol/L	1.7 mmol/L

Note. Bolded values indicate values outside of the defined reference range. BUN = blood urea nitrogen.

KS was admitted and started on broad-spectrum antibiotics with cefepime, vancomycin, and metronidazole for fever in an immunocompromised host. She was given fluid resuscitation and electrolyte repletion. Differential diagnoses related to her weakness, lethargy, and fevers included infection with possible blood stream infection; a gastrointestinal infection given presenting symptoms of nausea and diarrhea; and metabolic derangements given her severe kidney injury and electrolyte disturbances.

Within 24 hours, KS was noted to have worsening mental status, diffuse myoclonic jerks, and facial twitching despite the correction of electrolyte derangements. Blood cultures at this point had preliminarily been reported as positive with gram-negative rods, and she remained on appropriate antimicrobial coverage. Neurology was consulted given the change in exam, and an electroencephalogram (EEG) was recommended. This was negative for epileptiform activity. Given the identification of gram-negative rods on the blood culture, as well as a concern for cefepime neurotoxicity, she was switched to piperacillin/tazobactam. She continued to be intermittently febrile, and her mental status continued to decline with increased lethargy and limited ability to follow commands. The blood culture report was corrected and identified as growing gram-positive rods, with the final result as *Listeria monocytogenes*. Her antimicrobials were switched to gentamicin and ampicillin per recommendations from infectious disease colleagues. Due to her altered mental status, imaging was completed with a non-contrast CT of the head, which was negative for acute intracranial processes. An MRI of the brain was attempted; however, KS was unable to tolerate the exam.

Table 3. Initial Vital Signs

Temperature	38.8°C
Heart rate	136 beats per minute
Respiratory rate	30 breaths per minute
Blood pressure	177/88 mmHg
Oxygen saturation	94% on room air

DIFFERENTIAL DIAGNOSIS

WHAT IS THE MOST LIKELY DIAGNOSIS TO EXPLAIN KS' CONTINUED DECLINE ON NEUROLOGICAL EXAM?

- A ☐ Cefepime-induced neurotoxicity
- B ☐ Probable CNS manifestation from *Listeria* bacteremia
- C ☐ Hyponatremia

SEE BACK FOR ANSWER ▶

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A. Cefepime-induced neurotoxicity

B. Probable CNS manifestation from *Listeria* bacteremia (correct answer)

C. Hyponatremia

DISCUSSION

A Cefepime-induced neurotoxicity. Cefepime-induced neurotoxicity is well documented in the literature and was first described in 1999 (Payne et al., 2017). Cefepime-induced neurotoxicity often presents with altered mental status, reduced consciousness, myoclonus, and confusion (Payne et al., 2017). However, establishing a diagnosis remains difficult; it is often considered a diagnosis of exclusion and characterized by improvement following cessation of the drug. Electroencephalogram findings typically show abnormalities and can be described as exhibiting nonconvulsive status epilepticus, myoclonic status epilepticus, triphasic waves, and focal sharp waves (Payne et al., 2017). Risk factors for the development of cefepime-induced neurotoxicity include older age, renal dysfunction, critical illness, and altered blood-brain barrier (Payne et al., 2017).

While KS certainly had acute kidney injury on admission, cefepime was dosed appropriately for renal function. Cefepime-induced neurotoxicity was certainly high on the differential; however, KS did not have EEG findings consistent with what is described in the literature, and she did not have improvement following discontinuation of the drug. Therefore, cefepime-induced neurotoxicity was felt to be less likely, especially in light of new culture data suggesting *Listeria* infection, which would better explain her presentation.

B Probable central nervous system (CNS) manifestation from *Listeria* bacteremia (correct answer). *Listeria monocytogenes* is a gram-positive anaerobic bacterium that is most commonly transmitted to humans through the ingestion of contaminated foods. It typically affects individuals who are either immunocompromised, pregnant, elderly, or neonates (Moscatt et al., 2022). Infection with *Listeria monocytogenes* can have various forms of presentation. It can include manifestations with sepsis, meningitis, encephalitis, spontaneous abortion in pregnant individuals, fever, or self-limiting gastroenteritis (Rogalla & Bomar, 2022). Additionally, specific CNS symptoms may be present, including cranial nerve dysfunction, cerebellar abnormalities, and ataxia. In individuals with listeria meningitis, cerebrospinal fluid (CSF) analysis would typically reveal pleocytosis, reduced glucose, and increased protein levels. Gram stain with culture may show *Listeria monocytogenes*; however, this is often only cultured in one third of cases. If available, polymerase chain reaction may be more effective at yielding the diagnosis (Moscatt et al., 2022).

KS experienced fever and gastrointestinal symptoms in addition to progressive neurological decline with altered mental status and myoclonus. In light of her known *Listeria* bacteremia, it is likely that she had CNS involvement of her infection with listeria meningitis that we were unable to identify given the failed attempts at CSF collection with lumbar puncture.

C Hyponatremia. Although hyponatremia can be associated with altered mental status and is important to consider when working with a broad differential, KS' serum sodium levels were only marginally low on admission at 130 mmol/L and had subsequent improvement following hydration and electrolyte repletion. This is unlikely to be the cause of her progressive decline on her neurological exam.

MANAGEMENT

Following the change in her antibiotics to gentamicin and ampicillin, KS began to show clinical improvement, including improvement in her fever curve and mentation. Her repeat cultures remained without growth. Given her changes in mental status, there was a high concern that she had listeria meningoencephalitis. A lumbar puncture was attempted for diagnostic purposes, but it was unsuccessful. Given her clinical improvement

on the new antimicrobial regimen, further attempts were deferred. She was treated conservatively with a longer duration of antibiotics in light of the potential of listeria meningoencephalitis. She continued to improve clinically and was able to be discharged home on IV antibiotics to complete the full duration of treatment.

CONCLUSION

In this case, it is likely that KS' therapy with daratumumab for the treatment of her multiple myeloma increased her risk of infection, specifically for *Listeria*. Daratumumab is a CD38 monoclonal antibody that has been shown to be effective in the treatment of multiple myeloma. The mechanism of action involves binding to expressed CD38 myeloma cells and exhibits a cytotoxic effect. However, CD38 has also been shown to be crucial in the immune defense of *Listeria*, and this is by way of CD38 expression on activated macrophages that aid in this defensive response (Khan et al., 2020). There are preclinical data reports that support enhanced *Listeria* susceptibility in CD38 knockout mice (Khan et al., 2020).

In clinical practice, there have been case reports of patients with multiple myeloma on therapy with CD38 monoclonal antibodies such as daratumumab who develop listeriosis during their treatment. Furthermore, a retrospective study was performed at a medical center where a *Listeria* outbreak was noted. Of the patients who consumed food or drink from the eatery that was connected to this outbreak, seven patrons with listeriosis were noted to have been patients with a cancer diagnosis (Khan et al., 2020). Of those seven patients with cancer, four were patients with multiple myeloma, and of those four, three of them were receiving daratumumab-based therapy with pomalidomide (Pomalyst) and dexamethasone (Khan et al., 2020). The authors went on to report that while accounting for hospital visits, patients with multiple myeloma receiving therapy with daratumumab were at a 340-fold increased risk of developing listeriosis compared with all other patients with multiple myeloma (Khan et al., 2020).

With continued new drug development and the advancement in pharmacotherapies that act on targets and sites that may also play a significant role in the immune response, we must remain vigilant in our surveillance for a broad array of infections. We must also be aware of the targets that have been manipulated and their specific infection risks. With this information, we can thoughtfully consider if additional prophylaxis would be required to prevent infections that could have significant morbidity and mortality. In this case, it is well described that trimethoprim/sulfamethoxazole can be effective in the prevention of *Listeria* infections (Ueno et al., 2021). The decision to provide additional prophylaxis would need to be considered and weighed against the patient's other comorbidities and blood counts to determine if this would be appropriate from a risk-benefit standpoint. ●

Disclosure

The author has no conflicts of interest to disclose.

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